REMARKS

Claims 1-59 are pending, and claims 1-4, 6-14, 22-24, 26-39, and 48-59 are currently under consideration. Applicants add new claims 60-73. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants thank the Examiner for courtesies extended during a telephonic interview conducted on March 18, 2004.

1. Applicants note with appreciation that the finality of the previous rejection has been withdrawn in view of the request for continued examination filed July 16, 2003.

2-3. Claims 1-4, 6-14, 22-24, 26-39, and 48-59 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to make or use the claimed invention. Applicants traverse this rejection and maintain that the rejection is moot in light of the amended claims.

The basis of the rejection appears to be three-fold. First, the Examiner alleges that the specification fails to enable one of skill in the art to practice the claimed invention based on any route of administration. Second, the Examiner alleges that the specification fails to enable one of skill in the art to practice the invention based on administration of polypeptides comprising variant amino acid sequences. Third, the Examiner alleges that the specification fails to enable one of skill in the art to practice the invention based on in vivo administration of a polypeptide comprising one repeat of the hexameric sequence represented in SEQ ID NO: 1. Applicants contend that the specification provides a broadly enabling disclosure, and that each of the issues raised in the previous Office Action fail to undermine the patentability of the claimed invention.

With regard to the first grounds of rejection, Applicants begin by pointing out that although the prior Office Action did not explicitly state that this aspect of the rejection applied only to Applicants' method claims and not to Applicants' composition of matter claims, Applicants believe this to be the case. Applicants' composition of matter claims are defined with respect to a polypeptide component and a biocompatible support, and such compositions are further defined based on functional criteria. There is no doubt that one of skill in the art can

readily envision the claimed compositions. Furthermore, the application provides exemplary compositions that fall within the scope of these claims, and provides at least one working example of an elastin-based composition formulated on a biocompatible support and delivered in vivo to the artery of an animal (Examples 6-7; pages 56-58). Accordingly, and in compliance with the MPEP, the specification teaches at least one way to make and use the claimed invention that corresponds in scope to that of the present claims. Applicants contend that the specification is broadly enabling for pharmaceutical preparations of elastin-based compositions, and that the pending claims satisfy all of the requirements under 35 U.S.C. 112, first paragraph.

Furthermore, Applicants contend that any concerns that the Examiner may have had regarding the enablement of the claimed invention should have been obviated by Applicants' previous amendments to the claims that particularly pointed out that the claimed compositions are formulated in association with a biocompatible support and delivered to a target site. The dependent method claims are similarly limited. Accordingly, contrary to the Examiner's contention, the claims are directed to particular routes of administration.

While maintaining the rejection in the face of these amendments, the Examiner has offered no objective evidence to support the rejection. In accordance with MPEP 2164.04, "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention....A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained thereon which must be relied on for enabling support." (MPEP 2164.04; *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

Applicants contend that the claims are enabled throughout their scope, and respectfully submit that the Examiner has provided no objective evidence to undermine the patentability of the claimed subject matter. Reconsideration and withdrawal of this rejection are respectfully requested.

With regard to the second grounds of rejection, Applicants contend that the specification is broadly enabling for compositions comprising variant tropoelastin sequences, as well as methods of using such variant tropoelastin sequences. MPEP 2164.01 outlines the standard to be

used when assessing whether the claimed subject matter is enabled throughout its scope. The test for enablement is "whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." The MPEP further reminds us that the test of enablement does not require that one of skill in the art can practice the claimed invention without any experimentation. All that is required is that one of skill in the art can practice the claimed invention without undue experimentation.

Applicants previously indicated the extensive support and guidance provided in the specification regarding the making and testing of variant elastin-based polypeptides, as well as fragments of elastin-based compositions (page 17, line 14-page 20, line 23; page 22, lines 5-12; page 18, lines 4-9; page 20, lines 1-7). The guidance provided in the specification includes the disclosure of exemplary functional attributes that the claimed elastin-based compositions must possess, as well as a variety of in vitro and in vivo assays that can be used by one of skill in the art to readily evaluate whether a particular elastin-based composition does in fact possess the required functional activity (page 17, lines 14-25). Accordingly, based on the specification, one of skill in the art can readily make elastin-based compositions possessing a variant sequence, and test those polypeptides to identify those that possess the desired functional attributes (i.e., the bioactivity of naturally occurring sequence).

The Examiner points out that variation in amino acid sequence can sometimes have an impact on the function of a protein, and alleges that this possibility undermines the enablement of the claimed subject matter. The Examiner's argument is undermined by two points. First, the reference relied upon by the Examiner regarding the effect on protein function of changes in amino acid sequence was published substantially prior to the filing of the present application. Since that time, there has been a veritable explosion in the art of combinatorial chemistry which readily allows the making and testing of polypeptide variants without undue experimentation. Thus, even if one agrees that small differences in polypeptide sequence can affect the function of a protein or peptide, this point is immaterial in assessing the enablement of the claimed subject matter. Rather, the important consideration in determining whether Applicants have enabled the use of polypeptide variants in the subject methods is whether one of skill in the art could readily make and test polypeptide variants using the teachings of the specification and the state of the art, without undue experimentation, in order to select variants for use in the subject methods.

Applicants contend that this burden has been met. Enablement is assessed in terms of the level of skill in the art at the time of filing. Accordingly, as technical advances in a particular field occur, the amount of experimentation allowable without constituting undue experimentation increases. Such is the case here. The Examiner has cited additional, more recent publications that allegedly support the contention that changes in amino acid sequence can impact the activity of a protein. Once again, however, Applicants respectfully submit that this is not the issue. The issue is not whether the Examiner can find examples in the art where a change in amino acid sequence affected the function of the protein. The question is whether one of skill in the art, armed with the teachings of the present application, could readily make and test polypeptide variants that retain the functional properties of tropoelastin. The answer to this question is clear.

Additionally, however, Applicants do not rely on the high level of skill in the art alone. Experimentation provided in the specification indicates that the tropoelastin protein is amenable to variation in amino acid sequence. For example, tropoelastin isolated from a particular species retains its functional activity when administered in vitro or in vivo to cells or tissues from another species. The working examples provided in the present application use human tropoelastin (SEQ ID NO: 3) and a fragment of human tropoelastin containing seven repeats of SEQ ID NO: 1. Example 5 (page 55) demonstrates that the human tropoelastin protein and peptide retain functional activity in mouse cells. This, despite the fact that human and mouse tropoelastin are not identical. Examples 6-8 (pages 56-58) demonstrate that human tropoelastin protein and peptide retains functional activity in vivo in a rabbit system. This, despite the variation between the native human and rabbit sequences. Applicants contend that the working examples provided in the specification support the enablement of the presently claimed invention and support Applicants' contention that one of skill in the art can make and test variant polypeptides and fragments to identify variants and fragments that retain the biological activity of native tropoelastin.

MPEP 2164.06 and the courts have clearly articulated the standard for evaluating whether the level of experimentation necessary to practice the claimed invention is permissible. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d

1400, 1404 (Fed. Cir. 1988); *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicants contend that in light of the extensive guidance provided in the specification, and in light of the high level of skill in the art, one of skill in the art could readily make and test polypeptide variants to identify variants for use in the claimed invention without undue experimentation. Nevertheless, to expedite prosecution, Applicants have amended the claims and added new claims to more particularly point out the claimed subject matter. Specifically, Applicants have amended the claims to explicitly point out that fragments of SEQ ID NO: 3 (tropoelastin) that retain the biological activity of tropoelastin, and are suitable for use in the methods of the present invention, include one to seven repeats of the hexameric sequence represented in SEQ ID NO: 1. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The specification provides an extensive description of variant tropoelastin sequences and fragments, as well as methods of making and testing such variants and fragments. The specification provides ample evidence that tropoelastin is amenable to changes in amino acid sequence by demonstrating that tropoelastin from a particular species retains its functional activity when administered in vitro or in vivo to cells or tissues from another species. Finally, the level of skill in the art of making and testing polypeptide variants and fragments is very high, and thus one of skill in the art guided with the extensive teachings of the application would be able to make and test polypeptide variants and fragments without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

With regard to the third grounds of rejection, Applicants contend that the specification is broadly enabling for compositions comprising a single hexameric sequence represented in SEQ ID No. 1, as well as methods of using such compositions in vivo. Applicants previously submitted the declaration of Dean Li to demonstrate that, as detailed in the specification, elastin-based compositions comprising a single repeat of the hexameric sequence represented in SEQ ID NO: 1 retain the functional activity of native tropoelastin. In response to the post filing evidence, the Examiner appears to allege that the in vitro evidence is insufficient to support either Applicants' composition of matter claims or Applicants' method of use claims. Applicants respectfully disagree.

The specification provides working examples demonstrating that full length tropoelastin, or a fragment thereof comprising seven repeats of the hexameric sequence represented in SEQ ID NO: 1, function both in vitro and in vivo. On the basis of Applicants' evidence, the Examiner indicated in the previous Office Action that the claims were enabled for the use of an elastin-based composition comprising tropoelastin or seven repeats of the hexameric sequence represented in SEQ ID NO: 1. Applicants further provided post-filing evidence presented via the declaration of Dean Li demonstrating that an elastin-based composition comprising a single repeat of the hexameric sequence represented in SEQ ID NO: 1 retained the functional activity of tropoelastin when assayed in an in vitro system.

Tropoelastin, a composition comprising seven repeats of the hexameric sequence represented in SEQ ID NO: 1, or a composition comprising a single repeat of the hexameric sequence all function in vitro in vascular smooth muscle cells. Tropoelastin or a composition comprising seven repeats of the hexameric sequence represented in SEQ ID NO: 1 function in vivo. In light of this evidence, there is no reasonable basis to doubt that an elastin-based composition comprising one repeat of the hexameric sequence represented in SEQ ID NO: 1 that **retained** the functional activity of native tropoelastin **in vitro** would also retain the functional activity in vivo.

In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been satisfied.

Applicants contend that the specification is broadly enabling for a range of elastin-based compositions, as well as for numerous routes of administration of such elastin-based compositions. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out certain embodiments of Applicants' invention. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments and arguments of record, reconsideration and withdrawal of this rejection are respectfully requested.

4. Applicants take this opportunity to introduce new claims 60-73. Applicants respectfully submit that new claims 60-73 are free of the prior art, satisfy all of the conditions under 35 U.S.C. 112, and are in condition for allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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